

REMARKS

The present invention provides a nucleic acid construct for delivery of antisense nucleic acid sequences to cells for suppressing gene expression and methods of using the construct to suppress gene expression. A construct, having a 5' stem loop structure and a 3' stem loop structure on either side of an antisense nucleic acid sequence, targets a complementary nucleic acid sequence, *i.e.*, a mRNA sequence, thereby inhibiting gene expression.

In a preliminary matter in respect of the entire Office Action, it is noted that the Examiner has indicated in the Office Action Summary that claims 1-11 are pending and rejected, and in the Detailed Action of the Office Action, all paragraphs detailing the specific claim rejections therein, *i.e.*, paragraph numbers 2 and 4, refer to claims 1-11. However, Applicant respectfully submits that claims 1-15 are currently pending and under examination. Claims 1-15 were submitted in the application as filed and no restriction requirement has been made in the present application. Indeed, in the present Office Action, the Examiner refers to claims 13-15 by subject matter on page 3, paragraph 1 ("...and methods instantly claimed") and claims 13 and 15 by number on page 3, paragraph 2. It is therefore assumed that the Examiner intended to include claims 1-15 in the present Office Action, and therefore the remarks herein apply to claims 1-15. Claims 1-15 as filed are presented herein for the Examiner's convenience.

Double Patenting

The rejection of claims 1-15 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-11 of U.S. Patent No. 5,814,500, is respectfully traversed. However, in order to reduce the issues and expedite prosecution of the pending claims, Applicant will consider submitting a terminal disclaimer in compliance with 37 C.F.R. §1.321(c) to overcome the rejection once pending claims are allowed.

Rejection Under 35 U.S.C. §112, first paragraph

The rejection of claims 1-15 under 35 U.S.C. §112, first paragraph, as allegedly not providing enablement for the breadth of the nucleic acid constructs and methods instantly claimed is respectfully traversed.

Applicant respectfully disagrees with the Examiner's assertion that the specification "while being enabling for the scope of the invention as claimed in U.S. Patent No. 5,814,500, does not reasonably provide enablement for the breadth of nucleic acid constructs and methods instantly claimed." (Office Action, page 3, paragraph 1). Applicant submits that the specification provides ample support for the nucleic acid constructs and methods claimed.

The pessimistic statements about antisense nucleic acids presented in the Office Action are not an indication that antisense constructs or methods will not work. The potential of antisense oligonucleotides to selectively inhibit protein synthesis from a target gene of interest has generated a great deal of enthusiasm for their development in experimental therapeutics (*e.g.*, McShan, W.M., *et al.* (1992) *J. Biol. Chem.* 267:5712-21; Calbretta, B. (1991) *Cancer Res.* 51:4505-4510. Further, the production of antisense oligonucleotides has further been a subject of U.S. patents (*e.g.* Dietz, U.S. Patent No. 5,814,500; Noonberg *et al.* U.S. Patent No. 5,624,803).

The specification provides ample guidance for production of antisense oligonucleotides and triple helix oligonucleotides and recites methods for introduction of the antisense molecules into cells (page 13, lines 3 to page 14, line 7). Applicant submits that the introduction of nucleic acids into cells is routine to one skilled in the art. The Examiner notes that Flanagan *et al.* (*Nature Biotech* (1999) 17:48-52) find that "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues... Unfortunately, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)". However, Flanagan also notes that [t]he liver, kidney, and spleen

are the major sites for oligonucleotide accumulation" (page 51, column 2). When these organs are the intended target site, therapeutic methods using therapeutic oligonucleotides would indeed meet the "challenge of successful entry and localization to the intended target" (Office action, page 4, paragraph 1).

The Examiner asserts that *in vitro* transfection results are not predictive of *in vivo* success because *in vitro*, target specificity may be manipulated by changing hybridization conditions. Applicant submits that these comments are inapplicable to the present invention. Applicant presents data from successful *in vitro* transfections that were performed using a commercially available DOTAP liposome formulation according to manufacturer's instructions, *i.e.*, without extensive manipulation of conditions (Example 1: page 25, lines 26-28). Applicant also provides detailed information for performing liposome-mediated transfections *in vivo* (see page 13, line 3 to page 14, line 2). Applicant respectfully submits, in contrast to the Examiner's assertion (page 4 to page 5, bridging paragraph), that, based on the guidance provided by the specification, successful *in vitro* transfections can be correlated with successful *in vivo* delivery.

Applicant respectfully disagrees with the Examiner's assertion that "one of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art" (Office Action, page 5, first paragraph). Ample guidance is provided in the specification for delivery of invention construct into cells. For example, methods of delivery include using colloidal dispersion systems (page 13, line 3 to page 14, line 2), using a "naked expression vector" (page 14, lines 3-7) and using viral vectors (page 16, lines 11 to 28). Applicant submits that in view of the guidance provided in the specification, one could readily achieve successful delivery of invention constructs.

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Page 7

PATENT
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In summary, in view of the detailed methods and guidance provided by the Specification, and the level of skill in the art of antisense construction and delivery, Applicant respectfully submits that the grounds for the rejection under 35 U.S.C. § 112, first paragraph are moot.

In view of the remarks herein, reconsideration and favorable action on all pending claims, 1-15, are respectfully requested. In the event any matters remain to be resolved in view of this communication, Examiner is requested to telephone the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: _____

6/2/00



Lisa A Haile, Ph.D.

Reg. No. 38,347

Telephone: (858) 677-1456

Facsimile: (858) 677-1465

GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1600
San Diego, California 92121-2189